Remarks

Reconsideration is respectfully requested.

Statement of the Substance of the Interview

Applicants sincerely thank Examiner Nelson Clarence Blakely III and his supervisor, Examiner Ardin Marschel, for the very courteous and helpful interview granted to Applicants' representatives, (the undersigned, and also Chenghua Luo, Reg. No. 53,247), and to the attorney for Applicants' licensee, Kathryn Doyle, on January 26, 2010. Although Attorney Chenghua Luo's name is not listed on the Interview Summary form itself, Applicants note the Examiner acknowledged that she was also present on the continuation sheet. At the interview, Applicants' representatives were granted the opportunity to discuss the pending claims and the outstanding rejections. The interview summary as provided by the Examiner is correct except that Applicants discussed filing a Supplemental Reply (rather than a Supplemental Amendment) to correct and clarify two statements made in the Amendment and Reply filed November 12, 2009.

Supplemental Reply with Remarks to the Amendment and Reply filed November 12, 2009

As indicated at the interview, and as noted in Examiner's Interview Summary Form, (in the last sentence, that states that Applicants will be submitting a Supplemental Amendment to clarify the statements below), Applicants desire to clarify and correct two

sentences in the Remarks section of the Amendment and Reply filed November 12, 2009.

(A) Clarification of page 10, in paragraph 15

At page 10, in paragraph 15, in the Amendment and Reply filed November 12, 2009, Applicants stated:

> 15. It is clear from a reading of Gębicki that Gębicki's disclosure is focused entirely on treatment of skin, and DOES NOT disclose systemic treatment using 1-MNA. (Emphasis in original.)

However, this should read as follows:

> 15. It is clear from a reading of Gębicki that Gębicki's disclosure is focused entirely on treatment of skin, and DOES NOT disclose ***experiments showing*** systemic treatment using 1-MNA. (Emphasis in original; correction in bold and italics.)

This clarification is requested because at page 111, column 1, last paragraph, Gębicki speculates that 1-methylnicotinamide (MNA^+) introduced into blood circulation will interact with glycosaminoglycans that are located on a surface of vascular endothelium cells.

(B) Clarification of page 10, in paragraph 17

At page 10, in paragraph 17, in the Amendment and Reply filed November 12, 2009, Applicants stated, in part:

> . . . Oettgen teaches that 1-MNA and NA have an effect on an anti-neoplastic compound in mice.

However, that sentence should read:

> . . . Oettgen teaches that ***nicotinic acid*** and NA have an effect on an anti-neoplastic compound in mice. (Correction in bold and italics)

It is believed that the Supplemental Amendment to which Examiner refers is the above clarification, and not a formal amendment of the claims. Therefore, it is believed that the comments in this Supplemental Reply are sufficient to clarify the record and address Examiner's statement in the Interview Summary Form.

Applicants sincerely regret these in advertent errors and respectfully apologize for any confusion this has caused.

The Pending Claims

At the interview, the amended claims were discussed. As amended in the Amendment and Reply filed on November 12, 2009, claims 57, 58, 70, 71, 79, 87 and 90-93 are pending. Claims 90-93 are new.

The amended claims are directed to a method for treatment of hyperglyceridemia in a subject in need thereof by administering a pharmaceutically acceptable salt of 1-methylnicotinamide (1-MNA), wherein the administering lowers the subject's plasma triglyceride level.

The new claims are directed to a method of treating dyslipidemia in a subject in need thereof by administering a pharmaceutically acceptable salt of 1-methylnicotinamide (1-MNA), wherein the administering raises the subject's HDL level and lowers the subject's plasma triglyceride level.

The Rejections under 35 U.S.C. § 103(a)

At the interview, the rejections under 35 U.S.C. § 103(a) were reviewed and discussed.

The first rejection 35 U.S.C. § 103(a)

Claims 57, 58 and 87 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlson *et al., Atherosclerosis 16*:359-368 (1972) (herein "Carlson-1972"), in view

of Gębicki *et al., Polish J. Pharmacology 55*:109-112 (2003) (herein "Gębicki"), as evidenced by Oettgen *et al., Cancer Res. 20*:1597-1601 (1960) (herein " Oettgen").

The second rejection 35 U.S.C. § 103(a)

Claims 70, 71 and 79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlson in view of Gębicki as evidenced by Oettgen, as applied above, and further in view of Bova *et al.,* WO 99/06046 (herein "Bova"), and Mathias, U.S. Patent No. 7,153,870 B2 (herein "Mathias").

It was noted that Carlson-1972 is relied on, *inter alia*, as disclosing a case of massive hypertriglyceridemia with fasting triglycerides in one subject, wherein nicotinic acid or nicotinamide was administered to reduce plasma triglyceride levels to about 2-3 mmoles/L and raise the reduced levels of low-and high-density lipoproteins. Examiner states Carlson-1972 fails to disclose 1-MNA.

Gębicki is relied on, *inter alia*, as disclosing a homologue, or analog of 1-methylnicotinamide (1-MNA) as one of the two major primary metabolites of nicotinamide (NA).

Oettgen is relied on, *inter alia*, as disclosing charts wherein N-(hydroxymethyl)nicotinamide was equally as potent as nicotinamide and nicotinic acid in reversing the anti-neoplastic effect of thiadiazole on leukemia cells.

Bova is relived on, *inter alia*, as disclosing specific niacin formulations for treatment of hyperlipidemia.

Mathias is relived on, *inter alia*, as disclosing nicotinamide derivatives useful as phosphodiesterase inhibitors.

Additional documents discussed

The following additional documents were discussed at the interview:

Carlson, L.A., "Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review," *Journal of Internal Medicine 258*:94-114 (2005) (submitted to the Office in the Fifth Supplemental IDS as document NPL5, herein "Carlson-2005");

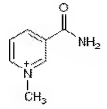
Dalton, C., *et al.*, "Relationship of nicotinamide and nicotinic acid to hypolipidemia," *Biochem. Pharma. 19*:2609-2619, (1970) (submitted to the Office in the Fifth Supplemental IDS as document NPL6, herein "Dalton"); and

Wise, A., et al., "Molecular identification of high and low affinity receptors for nicotinic acid," *J. Biol. Chem. 278*(11):9868-9874, (2003) (submitted to the Office in the Fifth Supplemental IDS as document NPL10, hereinafter "Wise").

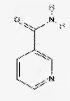
The Chemical Structures

At the interview, the structural formulae of 1-methylnicotinamide (1-MNA), nicotinamide (NA) and nicotinic acid (niacin) were shown and are copied below:

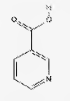
1-methylnicotinamide (1-MNA)



nicotinamide (NA)



nicotinic acid



As discussed at the interview, at the time of the invention, it was known in the art that nicotinic acid had the ability to lower plasma cholesterol, and alter the lipid profile in beneficial ways. But also, it was known that nicotinic acid had undesirable side effects, the most important of which was that administration of nicotinic acid was reported to be accompanied by an unpleasant flushing of the skin. Nicotinamide, which differs from nicotinic acid in the substitution of NH_2 for the OH, did not have the side effects of nicotinic acid, but also, was not active.

However, the compound 1-MNA, which, like nicotinamide, retains the substitution of NH_2 for the OH in the side chain, but also, contains a further change in which the ring nitrogen at position 1 is derivatized with a methyl group, not only, as discovered for the first time by the inventors, surprisingly recovered beneficial

cholesterol lowering and lipid profile altering effects of nicotinic acid (that had been lost with the very similar structure nicotinamide), but also, 1-MNA lacked the flushing side effect that occurred with nicotinic acid.

At the interview, Applicants first presented literature that supported Applicants' position that, at the time of the invention, it was known in the art that nicotinamide did not possess the ability to lower plasma cholesterol or alter lipid profiles as did nicotinic acid. To establish this, Applicants' undersigned attorney first discussed the a post-filing date review article, Carlson-2005. Although it is not known for certain, the author of the article, L. A. Carlson, appears to be the same author as that on the article cited by the Examiner (herein Carlson-1972).

Carlson-2005 reviews the history of the use of nicotinic acid (also known as niacin) since the 1950's and mentions articles that compared the activity of nicotinic acid with that of NA (nicotinamide). Specifically, Applicants' undersigned pointed the Examiner to the following in Carlson-2005:

> • Carlson-2005's first section, entitled, "The double-faced nicotinic acid" at pages 94-95 cites eight publications (Carlson-2005 references 1-8) that were published prior to Applicants' priority date that examine the ability of nicotinic acid to, inter alia, lower plasma cholesterol.
>
> • At page 94, column 2, Carlson-2005 states: "In the landmark study of 1955 Altschul *et al.* . . . reported that nicotinic acid in gram doses lowered plasma cholesterol in normal as well as hypercholesterolaemic subjects. Of considerable interest is that nicotinamide did not affect the plasma lipid levels. This is a remarkable observation as both nicotinic acid and nicotinamide, chemically quite alike, are nutritionally equivalent and known as vitamin B3. . . . The unexpected difference between nicotinic acid and nicotinamide may be due to the fact that while nicotinic acid

is a powerful inhibitor of fat-mobilizing lipolysis in adipose tissue, this property is not shared by nicotinamide. . . . "

- [In a trial conducted in 1959, nicotinic acid was found to decrease cholesterol level.] In this trial it was once again shown that nicotinamide in high doses did not lower plasma cholesterol. See Carlson 2005, p. 95, col. 2, lines 11-13.

- [Several articles published in 2001 and 2003 indicate the presence of a high-affinity receptor for nicotinic acid, and such a receptor may represent a mechanism for the rapid uptake of nicotinic acid in adipose tissue and its preferential distribution and accumulation in this tissue.] Of considerable interest is that nicotinamide, which does not share the lipid-metabolic effects of nicotinic acid, is not bound by this receptor. See Carlson 2005, p. 97, col. 2, first full paragraph.

Applicants discussed that the person of ordinary skill in the art would not have read Carlson-1972 in a vacuum. Rather, the person of ordinary skill in the art would have read Carlson-1972 with the understanding and knowledge of this earlier work mentioned above. When Carlson-1972 is read in combination with this earlier work, the only conclusion that could be reached is that although Carlson-1972 administers nicotinamide, it was most likely that nicotinamide itself was not the active agent, as further discussed below.

At the interview, Applicants undersigned attorney discussed that although Carlson-1972 reported one case wherein administration of nicotinamide reduced plasma triglyceride levels and raise the reduced levels of low-and high-density lipoproteins in one subject, the art indicates that such effects are, in fact, being caused by nicotinic acid (also called niacin). To further support that nicotinic acid/niacin (and not nicotinamide) was the active agent, in addition to the evidence in Carlson-2005, Dalton and Wise were discussed with the Examiner.

Dalton looked at NA (nicotinic acid) and niacin and their effects on hypolipidemia and concludes that "the lipopenic action of nicotinamide was indirect and was dependent upon deamidation to nicotinic acid." *See* Dalton, Abstract. See also, Dalton p. 2618 (lines 11-13), in which Dalton states, "It is concluded from this study that the hypolipidemic activity of NAM [Dalton's abbreviation for nicotinamide] should be attributed to the NA [Dalton's abbreviation for nicotinic acid] generated in these animals by deamidation of nicotinamide."

Also, Dalton suggests that nicotinamide preparations could have been contaminated with nicotinic acid. At Dalton page 2617, lines 1-3, Dalton states, "It should be noted that a 0.1 per cent contamination of NAM [nicotinamide] with NA [nicotinic acid] could account for the antilipolytic activity observed *in vitro*."

Applicants then discussed Wise. Wise discloses the identification of HM74 and HM74A, as being high and low affinity receptors respectively, for nicotinic acid (niacin). Wise states:

> Nicotinamide, which unlike nicotinic acid produces no alteration in lipoprotein profiles, . . . acted only as a very weak agonist at HM74A. Indeed, nicotinamide was ~1000-fold less potent than nicotinic acid, a level of activity that could be due to contaminant nicotinic acid (*e.g.*, 0.1%).

Wise, p. 9874, column 1, lines 7-12.

Thus, the totality of the art demonstrates that nicotinamide does not have hypolipodemic activity. The literature at the time of the invention establishes that the person of ordinary skill in the art who read Carlson-1972 would conclude that any

hypolipolytic activity observed in Carlson-1972 is indirectly caused by nicotinic acid/nacin, either due to deamidation of nicotinamide to nicotinic acid, or due to contamination of the nicotinamide with nicotinic acid.

Additionally, Applicants discussed that there is no evidence that 1-MNA converts to nicotinamide or niacin, so there is nothing to lead the artisan to even look to 1-MNA as a possible agent that possesses the ability to treat hypertriglyceridemia or dyslipidemia. Gębicki shows only the reverse reaction, that nicotinamide (abbreviated as NA in Gębicki) is degraded to 1-MNA (*See* Gębicki, p. 109 and Scheme 1), a reaction that leads away from the formation of nicotinic acid.

As discussed in the interview, the remaining documents cited by the Examiner do not cure the deficiency of Carlson-1972. In fact, several of the documents support that NA (nicotinamide) and 1-MNA have different activities. For example, Gębicki distinguishes the properties of 1-MNA and NA in at least two ways. Gębicki reports that 1-MNA, in contrast to NA, binds to glycosaminoglycans (Gębicki page 111, col. 1, last paragraph). In addition, although Gębicki reports that both 1-MNA and NA are poor scavengers of oxygen radicals, nevertheless, NA is more effective than 1-MNA in that regard. So, although 1-MNA is a metabolite of NA, nevertheless, Gębicki establishes that there are differences in the properties of the two compounds. Thus, the literature does not establish an expectation that a property that NA lacks as compared to nicotinic acid, and especially, the ability to treat hypertriglyceridemia or dyslipidemia, would be found in 1-MNA.

Oettgen compares the effects of NA and nicotinic acid and related compounds on the antineoplastic activity of thiadiazole. NA and nicotinic acid are antagonists of the antineoplastic activity of thaidiazole.

First, Applicants note that there is no nexus on the record between the anti-neoplastic effects of NA and nicotinic acid, and treatment of high triglyceride and hyperlipidemia. However, even accepting that there is no nexus, at the interview, Applicants drew the Examiner's attention to Oettgen Table 1.

In Table 1, Oettgen presents data that compare the ability of different compounds to reverse the anti-neoplastic effect of thiadiazole, to that of nicotinamide and nicotinic acid. One compound that was tested is N-methylnicotinamide. Oettgen reports that the compound N-methylnicotinamide lacked the ability to reverse thaidiazole's effect at doses that were up to 10 times the dose of nicotinic acid. *See* Oettgen, Table 1, p. 1600.

Applicants discussed that it is unclear from Oettgen whether the N-methylnicotinamide that Oettgen used is the compound that has the methyl group on the side chain, or on the ring structure. It is likely that it was on the side chain. However, even assuming that Oettgen's used N-methylnicotinamide that was derivatized with a methyl group in the side chain, the negative results reported by Oettgen leads the artisan away from finding a compound that acted like nicotinic acid by adding a methyl group anywhere else, and in particular, to the other nitrogen at the 1 position in the ring structure, much less to a suggestion that doing so would result in a compound that had the ability to treat hypertriglyceridemia or dyslipidemia.

Bova and Mathias are applied only against the claims that are directed to specific modes of administration, or in combination with a pharmaceutically acceptable carrier.

It was also discussed that Bova takes a completely different approach to the problem of how to reduce the side effects of nicotinic acid administration. Bova discloses reducing the side effects of nicotinic acid by combining it with a HMG-CoA reductase inhibitor in a specially formulated pharmaceutical formulation that has been engineered to provide for differential controlled release of each compound. Applicants noted that while Bova does list nicotinamide on page 15, at line 9, in the list of compounds that can be administered by his method, nevertheless, Bova does not present evidence that contract the reports mentioned in Carlson-2005, or that contract Dalton or Wise. Therefore, Bova does not cure the deficiencies of the cited art.

Also, as to Mathias, it was discussed that Mathias' derivatives are chemically complex, and are specifically useful as inhibitors of PDE4. Nothing in Mathias' disclosure of how to administer his derivatives cures the deficiencies of the combination of cited art, as discussed above.

In summary, as discussed at the interview, the literature that was available at the time of the invention establishes that nicotinamide itself does not possess the ability to alter blood cholesterol or plasma lipid profiles in a beneficial manner. Instead, any such activity, if observed, is likely to be due to the metabolic degradation to nicotinic acid *in vivo* and/or contamination of the preparation with nicotinic acid. The combination of the cited art does not lead to a suggestion or otherwise render obvious that modifying the structure of nicotinamide to add a methyl group to the ring nitrogen at position 1 would

result in a compound that not only is useful to treat hypertriglyceridemia and dyslipidemia, but also lacks the side effects of nicotinic acid. Therefore, in view of the totality of the art, Applicants respectfully assert that a person of ordinary skill in the art at the time of the invention would not have considered it obvious over the combination of the cited art to treat hypertriglycerdemia and dyslipidemia by administering 1-MNA. Accordingly, Applicants respectfully assert that the pending claims are unobvious. Reconsideration and withdrawal of the rejections are respectfully requested.

The provisional rejections for obviousness type double patenting

The rejection

Applicants' undersigned was also granted the opportunity to discuss the provisionally nonstatutory obviousness-type double patenting of claims 57, 58, 70, and 87 over claims 1, 5, 6 and 8 of copending application no. 11/874,627.

Discussion

As discussed at the interview, Applicants believe that the rejection is moot. Specifically, claim 1 of application no. 11/874,627 was amended to incorporate the embodiments of claim 2, which is not part of the double patenting rejection. Therefore, there are no conflicting claims between the present application and application no. 11/874,627.

Conclusion

It is respectfully believed that a full and complete reply to the Office action has been made and that this application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

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